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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/023,232	02/13/98	MONOSOV	A 312762001530

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EXAMINER	
BECKERLEG A	
ART UNIT	**PAPER NUMBER**
1632	15
DATE MAILED:	09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/023,232	MONOSOV ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment received on 4/12/01 has been entered. New claims 30-65 have been added. Claims 1-65 are pending in the instant application. Applicant's stated intention to surrender the original patent in the event the instant claims become allowable is acknowledged. An action on the merits follows.

Claim Rejections - 35 USC § 112

The rejection of amended, original, or new claims 19, 26, 29, 38-41, 50-53, and 62-65 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found sufficient to overcome the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that techniques for making immunodeficient mammals using radiation or immunosuppressant compounds were well known in the art and that the level of immunodeficiency is inherent in the model as claimed. As noted in the previous office action, the specification provides not specific guidance as to levels of irradiation, types of irradiation, or dosages and types of immunosuppressant compounds needed to create any type of non-human mammal with a degree of immunodeficiency sufficient to allow the implantation and growth of a foreign human tumor in the "immunodeficient" host such that the tumor growth mimics the

natural progression of the disease in a human. While the art at the time of filing does teach general methods of depleting immune responsiveness, the prior art does not teach the level and nature of immunodeficiency that would be required to sustain the growth of a xenogeneic tumor for a period of time sufficient to allow "natural" growth and metastasis. Further, the prior art does not teach genetically immunodeficient non-human mammals other than athymic nude mice or rats or SCID mice. The applicant is reminded the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Thus, the applicant's argument that the specification is enabled for the breadth of the claims because all of the requisite teachings to make and use the instant non-human mammals as models of human neoplastic disease can be found in the art is not supported either by the teachings of the

prior art or by the requirements for the fulfillment of 35 U.S.C. 112 first paragraph as interpreted by the Federal Circuit Court. Therefore, in view of the state of the art of immunodeficient non-human mammals at the time of filing, the lack of guidance provided by the specification concerning non-rodent athymic nude or SCID mammals suitable for use as a model of human neoplastic disease, the lack of guidance concerning the how to make any non-human mammal with a level of immunodeficiency sufficient to allow the physiological growth and metastasis of a human tumor, the lack of working examples using non-human mammals other than rodents, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The rejection of claims 1-29 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The rejection of original, amended, or new claims 1-13, 15, 17, 19-20, 22, 24, 26-29, and 31-65 under 35 U.S.C. 103 over Wang et al. in view of McLemore et al. and Otto et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

It is noted that the examiner apologizes for the typographical errors in listing the claims in the rejections under 35 U.S.C. 103 in the previous office action.

The applicant argues that neither Wang nor McLemore provide sufficient teachings that the implanted tumor cells metastasize according to the same patterns observed in humans, and that neither specifically teaches that the disclosed models are "faithful" models of human disease progression. As noted in the previous office action, Wang et al. clearly teaches that colon tumor cells orthotopically implanted within the colonic wall of nude mice, "... invaded the various subregions of the colonic wall and mimicked the original pattern characteristic for patient tumors" (Wang et al., page 331). The applicant is also reminded that the claims do not recite any specific limitation regarding the metastatic growth patterns of the implanted tumors or the time course over which the disease course is to be followed. The claims simply recite that the implanted tumor "mimics the progression of the neoplastic disease in the rodent". Wang explicitly teaches that the disclosed nude mouse model does just that. In regards to McLemore et al., the applicant argues that McLemore also does not teach the generation of distant metastases. McLemore, however, does teach that the orthotopic implantation of human lung tumor cells results in lung tumor growth characteristics and clinical symptoms similar those observed in the human lung cancer patients, and that both local and distant metastases were in fact observed (McLemore, page 5136, column 2, paragraph 2). Thus, both Wang et al. and McLemore et al. clearly teach that the orthotopic implantation of human tumors in nude mice results in growth characteristics similar to that observed in the human patient.

In regards to Otto et al., the applicant argues that there is no suggestion in Otto et al. to utilize the implantation of tumor pieces to make a model of disease progression and that Otto et al. is in fact addressing a different problem than that addressed by applicant's invention. It appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Further, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Note also that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). It has been held that a prior art reference must either

be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In this case, Otto et al. was cited for teaching methods of directly transplanting pieces of human tumor tissue into naive nude mice. Otto et al. was also cited for teaching that the growth of the transplanted human tumor tissue in the nude mouse correlated well with the clinical course of the human patients. As stated on pages 6-7, bridging sentence, of the previous office action, based on the teachings of Otto et al., that human neoplastic tissue can be transplanted directly from patients to nude mice and that the growth and morphology of the neoplastic tissue resembles that seen in the patient, the skilled artisan would have been motivated to transplant human neoplastic tissue rather than human neoplastic cells in suspension in order to save the time and effort of generating and maintaining human cell lines *in vitro* that retain the characteristics of the original tumor. Thus, the motivation to combine the teachings of Otto et al. with McLemore and Wang comes from the knowledge generally available to one of ordinary skill in the art that isolating and growing human tumor cells *in vitro* is time consuming and can be extremely difficult for certain tumor types.

Thus, in view of the benefits of using neoplastic tissue over a cell suspension, it would have been *prima facie* obvious to the skilled artisan to substitute intact tumor tissue for the tumor or cells taught by Wang et al. or McLemore et al. in the method of generating a nude mouse model of human cancer by orthotopic transplantation as taught by Wang et al. Furthermore, based

on the teachings of Otto et al. that intact tumor tissue maintains growth and morphological characteristics in the nude mouse, and the teachings of Wang et al. and McLemore et al. that orthotopic transplantation in nude mice versus subcutaneous transplantation more closely mimics the growth and metastases of human tumors in patients, the skilled artisan would have had a reasonable expectation of success in generating and using a nude mouse model for human neoplastic disease characterized by orthotopically transplanted intact colon or lung tissue. In addition, as the art of record teaches that many different types of tumor tissue, including colonic, lung, and renal tissue, can be transplanted orthotopically into mice to generate a mouse model for human neoplastic disease, it would have been *prima facie* obvious to the skilled artisan to generate a nude mouse model for any type of human cancer, including breast or ovarian cancer, by implanting the human neoplastic tissue into the analogous murine tissue. Therefore, in view of the high level of surgical skill in transplanting tissue into mice at the time of filing, the motivation to generate mouse models for many different kinds of human tumors by orthotopically transplanting human tumor tissue to nude or immunodeficient mice as provided by Wang et al., McLemore et al., and Otto et al., the skilled artisan would have had a reasonable expectation of success in implanting neoplastic human breast or ovarian tissue into murine breast or ovarian tissue respectively in order to produce a murine model for human breast or ovarian neoplastic disease.

The rejections of claims 14, 16, 21, and 23 under 35 U.S.C. 103 over Wang et al., McLemore et al., Otto et al. and Giovanella et al., and the rejection of claims 18 and 25 under 35 U.S.C. 103 over Wang et al., McLemore et al., Otto et al. and Reddy et al. are maintained. The applicant's arguments were directed solely to the applicability of the combination of Wang et al., McLemore et al., and Otto et al. These arguments have been addressed in detail above.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The art unit fax number is (703) 308-8724.

Dr. A.M.S. Beckerleg

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER